--35. (New) The method of claim 11, wherein the positive immune response comprises induction of Th2 lymphocytes reactive to the autoantigen.--

--36. (New) The method of claim 11, wherein the positive immune response comprises induction of non-pathogenic or suppressor Th lymphocytes reactive to the autoantigen.--

REMARKS

The present invention provides immunomodulating compositions for use in treating or preventing an autoimmune disorder comprising a nucleic acid construct encoding at least one epitope from a self-antigen and further encoding a biological response modifier in a pharmaceutically acceptable carrier. The invention further provides methods for inducing a positive regulatory immune response in a subject having or at risk of having an autoimmune disorder and methods for treating or preventing autoimmune disorders in a subject comprising administering to the subject an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from a self-antigen in a pharmaceutically acceptable carrier, wherein expression of the epitope generates in the subject a positive regulatory immune response, thereby treating or preventing the disorder.

Claims 1-31 were pending before this response. Claims 1-36 are currently pending, new claims 32-36 having been added by the present communication. In addition, claims 1, 2, 7-9, 11, 13, 18, 19, 20, 22-23, 28, and 29, have been amended herein to define Applicant's invention with greater particularity. These amendments add no new matter as the amended claim language is fully supported by the specification and original claims.

The Specification

The Examiner has requested amendment of the Specification to show proper use of the trademarks, for example ACCUCHECK III and TWEEN. In compliance, the Specification has been amended by the present communication to provide proper use of the trademarks METOPHANE, TWEEN AND ELISPOT. Applicant was unable to find ACCUCHECK III in the Specification and requests that the Examiner advise the location of this mark so that Applicant can correct any improper use of the mark that may exist.

The Sequence Listing

The Office Action asserts that the application fails to comply with the requirements of 37 CFR §1.821 through §1.825 for failure to provide a Sequence Listing as set forth in 37 CFR §1.821(a)(1) and (a)(2). To comply with the requirements of the statute and the Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures received herein, Applicant submits herewith a Sequence Listing **(one page)**, a copy of the sequence information in computer readable form, and a Statement Under 37 C.F.R. § 1.821(f) and (g) that the enclosed Sequence Listing includes no new matter. Applicant requests entry of the Sequence Listing in the application following Sheet 3 of the Figures.

The Requirement for Formal Drawings

The Office Action states that the application has been filed with informal drawings and that formal drawings will be required when the application is allowed. Applicant will comply with the requirement by submitting formal drawings upon receipt of a Notice of Allowance in this application.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-31 under 35 U.S.C. § 112, first paragraph, for alleged lack of an enabling disclosure. Applicant disagrees with the Examiner's assertion that practice of the invention would require undue experimentation. In particular, Applicant disagrees with the Examiner's assertion of the unpredictability of the present invention based upon a statement of Giannoukakis et al. regarding safety issues as follows: "Intervention aimed at limiting islet damage will become plausible only when more satisfactory risk prediction protocols are developed. However, some safe preventive measures have already been explored in animals models and may eventually be applied to humans" (Office Action, page 4; emphasis added). Applicant respectfully submits that the subject of safety is the purview of the FDA with reference to clinical trials and is not properly the concern of the PTO in determining whether a claim is enabled. *See, Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994): ("[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].") Applicant asks that the PTO make a careful, objective assessment of the issues it is competent to decide, such as whether an Applicant has provided some objective data to support an otherwise inherently incredible claim. This determination should be a threshold one, however, and not an ultimate answer to the question of whether the proposed invention is "safe and efficacious". Those judgments are reserved by statute for the U.S. Food and Drug Administration.

Moreover, Applicant disagrees with the Examiner's reliance upon a statement by Giannoukakis et al. regarding islet engraftment, as follows: "[a] better understanding of the genetics, the environmental triggers, and the immunopathology of type I diabetes, together with the factors affecting islet engraftment, as well as allogeneic and xenogeneic tolerance and protection from immune destruction, is necessary for these approaches to find clinical use" (Office Action, page 4; (See Giannoukakis, page 2117). Giannoukakis' statement pertains to a

procedure involving islet engraftment, an approach to treatment of diabetes wherein the subject's body processes are supplemented by introduction of foreign cells that produce a biologically active substance, insulin. In contrast, in the present invention, the subject is transiently transfected (i.e. genetic immunization) with polynucleotides that encode an immunogenic substance, an antigen, that is not administered for its biological activity, but which the subject "perceives" as foreign so as to raise "a positive regulatory immune response." Thus, the question of the body's rejection of foreign islet cells and/or DNA in a gene therapy-like application considered by Giannoukakis does not apply to the present invention, as defined by claims 1, 11 and 22. Those of skill in the art could readily provide nucleic acid encoding such an epitope for a human subject that would generate "a positive regulatory immune response" in a subject to which it is administered.

While acknowledging that the Specification provides guidance that demonstrates "treatment of a mouse model system for diabetes, along with experimental data for the treatment of diabetes in a mouse model system. (Office Action, page 4), the Examiner asserts: "Only prophetic guidance is provided for other autoimmune disorders" (Office Action, page 4). However, the Specification teaches that the concept of treating or preventing an autoimmune disorder by down regulation of autoreactive immune cells through the induction of appropriate biological response modifiers by an expressed self-epitope is a *general concept* applicable to any type of autoimmune disease that is associated with a self-antigen. In addition, as is known in the art, the response of the immune system to epitopes of antigens that are treated as "foreign", such as self-antigens, is known to be universal across species and, therefore, reasonably predictable. Thus, the cellular mechanism upon which the invention is based is not limited to self-antigens that cause diabetes. Accordingly, Applicant submits that undue experimentation would not be required by those of skill in the art to utilize the invention in treatment of a disease other than diabetes.

Furthermore, Applicant submits that undue experimentation would not be required to extend the invention from mice to another species. The Specification addresses this very point:

> the success of implementing laboratory animal models is predicated on the understanding that immunodominant epitopes are frequently active in different host species. Thus, an immunogenic determinant in one species, for example a rodent or pig, will generally be immunoreactive in a different species such as in humans.

(Specification, page 36, lines 28-32). Autoantigens encompassing immunodominant epitopes involved in pathogenesis are usually the same in animal models and humans. For example, insulin and GAD are autoantigens in type 1 diabetes in humans and in spontaneous animal models (i.e., non-obese diabetic mice). Given the level of knowledge in the art at the time the present application was filed, those of skill in the art would know how to prepare nucleic acid encoding an epitope of a self-antigen as well as that encoding any biological response modifier used in the invention compositions and methods that would be fully compatible with the subject to be treated, whether mouse or human. For example, Applicant discloses a number of different "expressed epitopes" useful for treating multiple sclerosis and diabetes (Specification, page 34, lines 4-17). Additional epitopes are known in the art and will be discovered in the future. In addition, nucleic acid encoding fully human cytokines and chemokines was known at the filing date of the present invention (Specification, page 27, line 24 to page 28, line 16).

Based upon the above arguments, Applicant submits that the present Specification provides sufficient objective data to fully enable the subject matter of present claims 1-5 and 7-35 and reconsideration of the present rejection for lack of enablement is therefore respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 6, 8, 9, 17, 19, 20, 27, 29 and 30 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. With regard to the Examiner's assertion that the term "biological response modifier" in claims 6, 17 and 27 is allegedly "not an art recognized term and no definition is provided in the claims and specification " (Office Action, page 5), Applicant respectfully submits that the Specification provides a full discussion of the meaning of the term as used in the claims at issue. The Specification teaches that biological response modifiers (BRMs) are a variety of "immunopotentiating agents" that stimulate the immune system without specificity (Specification, page 26, lines 24-25). For example, biological response modifiers include "agents that may not be immunogenic to the host, but nevertheless potentiate immunity by activating or enhancing the activity of cells of the immune system, such as T lymphocytes, natural killer cells, or lymphokine activated killer (LAK) cells (Specification, page 27, lines 25-27). Accordingly, the Specification teaches that cytokines and chemokines are examples of the "biological response modifiers" useful in the invention immunomodulating compositions and in practice of the invention methods (see Specification, page 34, line 21 to page 35, line 19). BRMs have activity on immune cells without binding to T cell or B cell antigen receptors.

With regard to the rejection of claims 8, 19 and 29 for alleged indefiniteness in failing to embody "proper use of the Markush format" (Office Action, page 5), Applicant has amended claims 8, 29 and 29 to recite a Markush group that follows the formula that recites members of the group as being "selected from the group consisting of A, B and C" as recommended by the Examiner.

With regard to the rejection of claims 9, 20 and 30 as allegedly being indefinite due to use of the phrase "regulatory element," Applicant traverses the Examiner's assertion that: "'Regulatory element' is not an art recognized term, and no definition is provided in the claims and specification to inform one of skill in the art exactly what is meant by this term" (Office Action, pages 5-6). Applicant respectfully submits that the term "regulatory element," as used in connection with nucleic acid sequences, has a well understood meaning in the art (e.g., a promoter). In addition, the Specification contains a full description of the meaning of the term as used in the present invention (see Specification, page 13, line 21 to page 15, line 2). However, to further define the meaning of the term "regulatory element" as used therein, claims 8, 19 and 29 have been amended to require that the regulatory element is "operatively linked to nucleic acid encoding the at least one epitope or the biological response modifier."

The Rejection under 35 U.S.C. § 102

Applicant's invention immunomodulating composition for use in treating or preventing an autoimmune disorder, as defined by present claim 1, distinguishes over the disclosure of each of the allegedly anticipating references cited by comprising a nucleic acid construct encoding at least one epitope from a self-antigen in a pharmaceutically acceptable carrier. Applicant's invention method for treating or preventing autoimmune disorder in a subject having or at risk of having the disorder, as defined by claim 11, distinguishes over the disclosure of each of the allegedly anticipating references cited by requiring administration to the subject of an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from a self-antigen "wherein expression of the epitope in the subject generates a positive regulatory immune response, thereby treating or preventing the disorder." Applicant's invention method for inducing a regulatory immune response in a subject having or at risk of having an autoimmune disorder, as defined by claim 22, distinguishes over each of the allegedly anticipating references cited by requiring administering to the subject an immunomodulatory

effective amount of a nucleic acid construct encoding at least one epitope from a self-antigen in a pharmaceutically acceptable carrier, wherein expression of the epitope in the subject generates a positive regulatory immune response.

Thus, claims 1, 11 and 22, all pertain to embodiments of the invention wherein the therapeutic effect of treatment or prevention of an autoimmune disease results from the epitope of a self-antigen, and the method claims further require the epitope to stimulate a "positive regulatory" immune response (e.g., a Th2 response) that treats an already existing disorder or prevents development of the disorder in an individual at risk of developing the disorder. Applicant defines a "self-antigen epitope" as follows:

> ... a peptide or protein against which an immune response can be elicited. The self-antigen epitope(s) is an immunogenic peptide protein fragment or protein derived from an autoreactive antigen or a cell involved in autoimmune disease. The immune response directed against the epitope or protein will protect the individual against the specific infection or disease with which the self-antigen epitope(s) is associated.

(Specification, page 12, lines 26-31). In addition, as is well understood in the art, each autoimmune disease is characterized by an immune response directed at one or more self antigens; whereas normally there are no active immune responses to self antigens, and no symptoms appear (See, WO 97/46253, page 17, of record herein).

A. Prud'homme

Applicant respectfully traverses the rejection of claims 1, 2, 5, 7-11, 13, 16-23 and 26-31 under 35 U.S.C. § 102(b) for allegedly being anticipated by Prud'homme et al. (*Gene Therapy* 6:771-777,1999; hereinafter "Prud'homme").

In contrast to Applicant's invention as described above, the Prud'homme composition contains a fusion protein whose protein units include the extracellular portion of the murine high affinity IFNγ receptor alpha chain and a mouse IgG1 heavy chain (Prud'homme, page 771, col. 2). There is no indication in Prud'homme that either high affinity IFNγ receptor or IgG1 heavy chain is or contains a self-antigen having at least one epitope associated with an autoimmune disease. IFNγ is a cytokine and is found in mammals that do not have an autoimmune disease. Thus, the Prud'homme construct does not contain a self-antigen and the balance of the construct used in Prud'homme's methods is said to be "constructed from non-immunogenic self elements, avoiding a neutralizing immune response" (Prud'homme, Abstract). Thus, the Prud'homme construct also fails to suggest use of a nucleic acid construct encoding an immunogenic epitope in treatment of an autoimmune disease. Hence, Applicant submits that Prud'homme does not disclose each and every element of claim 1, as would be required for anticipation under 35 USC § 102, and does not suggest Applicant's composition, as would be required for prima facie obviousness of claim 1 under 35 USC § 103.

Further, Prud'homme fails to disclose a method of using a construct containing an immunostimulatory epitope to raise a positive regulatory immune response in the subject to which it is administered. Generation of a "regulatory" immune response, as required by Applicant's method claims, is understood in the art to involve the Th2 response; whereas IFNγ is generally considered to be the associated with the Th1 immune response. Hence, Applicant respectfully submits that Prud'homme not only fails to disclose each and every element of claims 1, 2, 5, 7-11, 13, 16-23 and 26-31, as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b), but also teaches away from the invention.

Moreover, in view of the silence of Prud'homme regarding use of an epitope of a self-antigen in treatment of autoimmune disorders, and the emphasis upon avoiding immunogenic self elements in the treatment construct, an approach opposite to that of Applicant's invention wherein an epitope of a self-antigen is used to induce "a positive regulatory immune response" in treatment or prevention of an autoimmune disorder, Applicant submits that no suggestion is provided by Prud'homme to modify the disclosed construct to encode an epitope of a self-antigen for use in a treatment method that results in a positive regulatory immune response. In addition, Prud'homme fails to suggest generation in the subject of a positive immune response comprising proliferation of T-cells autoreactive to the antigen, as required in new claim 34, or proliferation of Th2 lymphocytes autoreactive to the antigen, as required in new claim 35. Accordingly, Applicant submits that Prud'homme fails to anticipate or suggest the subject matter of method claims 11-35 under 35 U.S.C.§ 103.

B. WO 97/46253

Applicant respectfully traverses the rejection of claims 1, 2, 9, 11, 13, 16, 20, 22, 23 and 30 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 97/46253; hereinafter "'253"). Applicant disagrees with the Examiner's assertion that:

> WO97/46253 taught (see especially the abstract, pages 13, 16, 17, 19-22, 35-37 and example 4) a nucleic acid which encoded a self-antigen in a plasmid construct under the control of a promoter which was administered to a mouse model system to protect the mice form onset of autoimmune disorders. The construct comprised a nucleic acid sequence which encoded cytokines.

(Office Action, page 7). After review of all cited passages of the reference, Applicant could not find any mention in '253 of a construct that comprises a nucleic acid sequence encoding a cytokine, as alleged by the Examiner in the passage quoted above, much less mention of one

encoding an epitope of a self-antigen. Accordingly, it is the position of the Applicant that '253 fails to disclose each and every element of Applicant's claim 1.

Regarding methods of treating autoimmune disease, the method of the '253 reference differs from Applicant's claimed method by disclosing that vectors or particles encoding an epitope of a self-antigen are required to be administered according to a regimen designed to elicit "either a reduction in a cytotoxic immune response or a desensitizing immune response is induced in the mammal" ('253, page 13, top). '253 further discloses that the antigen containing the epitope of interest is repeatedly delivered to the subject over a long period of time to induce desensitization and decrease cytotoxic T-cell responses ('253, page 34, lines 24-33; emphasis added). Thus, by advocacy of methods that cause desensitization, '253 fails to disclose or suggest the generation of a "positive regulatory immune response" in the subject, as is required in Applicant's method claims 11 and 22. In addition, '253 fails to disclose or suggest generation in the subject of a positive immune response comprising proliferation of T-cells autoreactive to the antigen, as required in new claim 34, or proliferation of Th2 lymphocytes autoreactive to the antigen, as required in new claim 35.

Accordingly, Applicant submits that the '253 reference fails either to disclose each and every element of the present claims, as would be required to establish anticipation under 35 U.S.C.§ 102, or to suggest the subject matter of the present invention so as to render the present claims *prima facie* obvious under 35 U.S.C.§ 103.

C. Ally

Applicant respectfully traverses the rejection of claims 1, 2, 5, 9, 11, 13, 16, 20, 22, 23 and 30 under 35 U.S.C. § 102(b), for allegedly being anticipated by Ally et al. (*J Immunol.* 155:5404-5408, 1995; hereinafter "Ally").

By contrast, to Applicant's invention as described above, Ally discloses plasmid constructs that encode a pancreatic self antigen, but are intended for ex vivo administration to bone marrow cells and hence are not suitable "for use in treating or preventing an autoimmune disorder" as is required in Applicant's claim 1. Hence, Ally fails to disclose each and every element of Applicant's composition according to claim 1.

With regard to the methods for treating autoimmune disorder in a mouse model, Ally discloses tolerization "primarily by clonal deletion" (Ally, page 5406, Col 1 bottom) of the Gp-specific T cells induced by expression of LCMV-gp in the transgenic mice. Thus, in Ally's method the T cells that recognize the self-antigen are deleted from the clonal repertoire; whereas in Applicant's invention, as defined by claims 11 and 22, a "positive regulatory immune response" is required to be generated. Applicant's method does not eliminate the self epitope-specific T cells directed against the vaccine, as shown by the results illustrated in Figure 3 of the Specification, wherein the level of T cells specific for the therapeutic self-antigen epitope (in this case, derived from the insulin B chain) are greatly increased (See also Table 3, page 43). Hence, Applicant respectfully submits that Ally fails to disclose generation of a positive regulatory immune response, and therefore fails to disclose each and every element of the invention method claims, as would be required to support a rejection under 35 U.S.C. § 102.

Moreover, Applicant respectfully submits that Ally fails to even suggest the present invention. Ally's emphasis upon "tolerization" by "clonal deletion" of T cells reactive to an epitope of the self-antigen administered as the therapeutic agent, is an approach opposite to that of Applicant's invention (i.e. one wherein a positive regulatory immune response is induced in treatment or prevention of an autoimmune disorder). In particular, Ally fails to suggest that generation in the subject of a positive immune response comprising proliferation of T-cells

autoreactive to the therapeutic self-antigen, as required in claim 34, or proliferation of Th2 lymphocytes autoreactive to the therapeutic self-antigen, as required in claim 35. Therefore, Applicant submits that Ally also provides no suggestion or motivation for modifying the disclosed tolerization technique or the constructs used therein so as to arrive at Applicant's constructs and methods of eliciting a positive regulatory immune response. Accordingly, Applicant submits that Ally fails to teach or suggest the subject matter of the present claims *prima facie* obvious under 35 U.S.C.§ 103.

D. WO 95/06718

Applicant respectfully traverses the rejection of claims 1, 2, 9, 11, 13, 16, 20, 22, 23 and 30 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 95/06718; hereinafter "'718"). By contrast, to Applicant's invention as described above, the epitope contained in the nucleic acid construct disclosed by '718 is not an epitope of a "self-antigen" as the term is used in Applicant's Specification and claims. Instead, '718 discloses "a vector construct that expresses "a protein or an active portion of a protein capable of inhibiting MHC antigen presentation, such that an autoimmune response against the cells is suppressed" ('718, page 6). Alternatively, the '718 recombinant vector construct expresses an antisense message or a ribozyme capable of inhibiting MHC antigen presentation ('718, page 6 bottom to page 7 top). Thus, Applicant respectfully submits that '718 fails to disclose a composition for use in treating or preventing an autoimmune disorder comprising a polynucleotide encoding a "self-antigen," as the term as understood in the art and as used in Applicant's Specification and claims. Thus the '718 application fails to disclose each and every element of the present claims as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b).

Moreover, this reference places great emphasis upon inhibiting MHC antigen presentation as a means of treating an autoimmune disorder, an approach opposite to that of Applicant's invention wherein a positive regulatory immune response is induced. In particular, in new claims 34 and 35, respectively, it is required that the positive regulatory immune response involve proliferation of T-cells autoreactive to the antigen or proliferation of Th2 lymphocytes autoreactive to the antigen. Therefore, Applicant submits that no suggestion is provided by '718 to modify the disclosed construct to encode an epitope of a self-antigen for use in a treatment method that results in a positive regulatory immune response. Accordingly, Applicant submits that the '718 reference fails to teach or suggest the subject matter of the present invention so as to render the present claims *prima facie* obvious under 35 U.S.C.§ 103.

E. WO 98/24908

Applicant respectfully traverses the rejection of claims 1, 2, 5-7, 9, 11-13, 16-18, 20, 22, 23 and 26-30 under 35 U.S.C. § 102(b), for allegedly being anticipated by WO 98/24908; hereinafter "'908"). (Note: the rejection is actually asserted against claims "36-30" rather than "26-30," but Applicant's response is based upon the assumption that "36-30" contains a typographical error. If this assumption is in error, Applicant requests clarification from the Examiner)

Applicant disagrees with the Examiner's assertion that: "WO 98/24908 taught ... the administration of a vector which contained a nucleic acid which encoded a self-antigen to treat autoimmune diseases and a nucleic acid encoding a cytokine such as interferon γ may be administered" (Office Action, page 8). Applicant respectfully submits that the '908 construct contains nucleic acid encoding a chemokine, CKβ13, or a CKβ13 polypeptide. However, '908 is silent regarding a vector containing nucleic acid encoding an epitope of a "self-antigen" as the

term is understood in the art and as used in Applicant's Specification and claims. In fact, it is known in the art that chemokines, such as CKβ13, participate in immune responses in normal individuals not having an autoimmune disorder. Further, self-antigens are molecules that play a critical role in the pathogenesis of autoimmune diseases, being recognized by pathogenic T cells via antigen receptors. This is in contrast with molecules like cytokines (e.g., IFN-γ) or chemokines (e.g., Ckβ13) that bind to non-antigen receptors in circumstances not necessarily associated with auto-immunity. Thus, Applicant respectfully submits that the '908 application fails to disclose each and every element of claims 1, 2, 5-7, 9, 11-13, 16-18, 20, 22, 23 and 26-30 as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b).

Moreover, in view of the absence of any teaching regarding use of a self-antigen in manipulation of immune responses in treatment of autoimmune disorders in this reference, Applicant submits that no suggestion is provided by '908 to modify the disclosed construct to encode an epitope of a self-antigen for use in a treatment method that results in a positive regulatory immune response. Accordingly, Applicant submits that the '908 reference fails to teach or suggest the subject matter of the present invention so as to render claims 1, 11 or 22 *prima facie* obvious under 35 U.S.C.§ 103.

F. WO 95/21926

Applicant respectfully traverses the rejection of claims 1, 4, 11, 12, 15, 16, 22, 25, 26 and 30 under 35 U.S.C. § 102(b), for allegedly being anticipated by WO 95/21926 (hereinafter "'926").

By contrast, to Applicant's invention as described above, '926 fails to disclose a nucleic acid sequence encoding an epitope of a "self-antigen" as the term is understood in the art and as used in the Specification and claims herein. Instead, '926 discloses that a sequence encoding a"

tolerogenic" epitope is to be placed at the N-terminus variable region of an immunoglobulin-encoding sequence. The definition of a "tolerogenic epitope" provided by '926 is as follows:

> an epitope that can induce immunological unresponsiveness to the epitope and or an antigen containing an epitope. A tolerogenic epitope is selected because of a desire to induce immunological unresponsiveness to the epitope and/or antigen containing the epitope.

('926, page 6, lines 27-31). In treatment of autoimmune disorders, '926 discloses use of the constructs to induce "tolerization" to the presence of the epitope of a self-antigen. "Tolerance" is described as a 2-fold to 100-fold decrease in antibody or lymphocyte responsiveness to the self-epitope ('926, page 19, lines 25-29).

Thus, the epitope contained in the '926 construct is not a "self-antigen" as the term is used in the art and in Applicant's Specification and claims. Further, the epitope selected for use in the method of '926 involves a down-regulation of immune system activity. Thus, '926 is absolutely silent regarding methods for administering a nucleic acid construct encoding an epitope of a self-antigen so as to generate a positive regulatory immune response in the subject. Accordingly, Applicant respectfully submits that '926 fails to disclose each and every element of Applicant's method claims 11 and 22 as would be required to support a rejection under 35 U.S.C. § 102(b).

Moreover, in view of the emphasis this reference places upon tolerization of the subject to the self-antigen, an approach opposite to that of Applicant's invention, Applicant submits that no suggestion is provided by '926 to modify the disclosed construct to encode a self-antigen selected for the purpose of inducing a positive regulatory immune response in a subject in prevention or treatment of an autoimmune disease. Accordingly, Applicant submits that the '926 reference would also fail to suggest the subject matter of the present invention so as to render claims 1, 11 or 22 *prima facie* obvious under 35 U.S.C.§ 103.

The Liu Reference

In a Supplemental Information Disclosure Statement submitted herewith, Applicant submits for the Examiner's consideration in determination of the patentability of the present invention a newly discovered reference by Jingxue Liu et al. (*Gene Ther Mol Biol* 3:197-206, 1998; hereinafter "Liu"). In contrast to Applicant's immunomodulating compositions, as described above, Liu discloses a nucleic acid construct encoding a truncated version of human glutamic acid decarboxylase 65 (GAD65) and the leader peptide (i.e., the first 23 amino acids) of IL-2 (See Liu, Materials and Methods, page 203). The function of the IL-2 leader peptide, according to Liu, is to cause secretion by mammalian cells of normally intracellular proteins (Liu, page 198, Col 2). Liu fails to disclose that the IL-2 leader peptide functions as a "biological response modifier" (i.e., possesses the cytokine function of IL-2). Thus Applicant respectfully submits that Liu fails to disclose a nucleic acid sequence encoding an epitope of a self-antigen, as would be necessary to anticipate composition claim 1, or a self-antigen and a biological response modifier, such as a cytokine or a chemokine, as would be required to anticipate claim 6.

In addition, Liu fails to suggest that a nucleic acid construct encoding an epitope of a self-antigen (with optional a biological response modifier) would have therapeutic utility for "treating or preventing an autoimmune disorder," as is required for Applicant's compositions. In Liu's nucleic acid construct the IL-2 derived sequence is only a "leader peptide" whose function normally is to facilitate passage through a membrane, such as insertion into membranes of the endoplasmic reticulum, as is known in the art (See for example, Lewin et al., *genes VII,* Oxford University Press, New York, 2000, Glossary). Thus, Applicant respectfully submits that Lui would also fail to suggest Applicant's compositions under 35 USC § 103.

In contrast to Applicant's invention methods for treatment or prevention of an autoimmune disorder, as described above, Liu discloses only that intramuscular injection of the GAD65- containing nucleic acid constructs to NOD mice resulted in a reduction of insulitis as determined by infiltration data obtained previous to the diabetic stage (i.e., at 10 weeks post administration). In addition, since Liu's data obtained concerning T-cell infiltration of islet cells is heterogeneous (lumping together pathogenic, non-pathogenic and even suppressor elements) Liu's overall infiltration scores are not determinative and may be misleading.

In the NOD model, the usual onset of diabetes in naïve mice is about 12-14 weeks, with approximately 70-90% of the animals reaching the diabetic stage around 30 weeks. (Note that Liu projects manifest diabetes at "250 days of age," page 198 Col. 1.) Thus, Liu's premature results obtained at 10 weeks fail to show whether the treatment administered would have an effect on disease suppression/infiltration during the diabetic stage of the disease. One should wonder why no data on disease suppression/infiltration during the diabetic stage in the mouse model were provided by Liu.

Accordingly, Applicant respectfully submits that Liu fails to provide an enabling disclosure of Applicant's compositions or methods for treating autoimmune diseases, making the Lui reference insufficient to establish anticipation of Applicant's general method for treating autoimmune diseases and conditions, even with regard to a single autoimmune disease, such as diabetes.

In addition, Applicant respectfully submits that Liu would fail to suggest the invention treatment methods to those of skill in the art under 35 USC § 103. At best, Liu's disclosure is an invitation to try the approach of testing the effect of intramuscular immunization of naked DNA

in the NOD mouse model. For example, Liu concludes that "injection of DNA encoding these proteins [GAD65] ... suggest[s] the possibility that this form of gene therapy might be useful to prevent clinical manifestation of IDDM" (Liu, page 198, Col. 2). However, "obvious to try" has never been the standard under 35 USC § 103. Accordingly, Applicant respectfully submits that the methods of claims 11-35 are not *prima facie* obvious in view of Liu.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on claims 1-5 and 7-35 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 4/20/00

Lisa A. Haile, Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY, CARY, WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, California 92121-2189